

Appl. No. 09/916,017  
Amdt. dated Monday, September 15, 2003  
Reply to Action dated August 27, 2003

This listing of claims will replace all prior versions and listings of claims in the application:

**Listing of Claims:**

- Claim 1. (withdrawn) A method for inhibiting metastatic tumors in a mammal suffering from one or more metastatic tumors, said method comprising administering to the mammal a therapeutically effective amount of a DNA sequence comprising a constitutive promoter operatively linked to a transcription sequence; wherein the transcription sequence, when transcribed, produces a messenger RNA sequence that comprises a translatable sequence encoding a toxin, and an untranslated sequence; wherein the untranslated sequence inhibits translation of the toxin sequence in the absence of eukaryotic initiation factor eIF4E, and wherein the untranslated sequence allows translation of the toxin sequence into a toxin in the presence of eukaryotic initiation factor eIF4E.
- Claim 2. (withdrawn) A method as recited in Claim 1, wherein the untranslated region comprises the 5' untranslated sequence of fibroblast growth factor-2; whereby, in a metastatic tumor cell in which the presence of eukaryotic initiation factor eIF4E allows the translation of the toxin, the toxin is translated to kill the tumor cell; and whereby the majority of non-tumor cells in the mammal are not killed due to the low levels of eukaryotic initiation factor eIF4E typically present in non-tumor cells.
- Claim 3. (withdrawn) A method as recited in Claim 1, wherein the untranslated region comprises the 5' untranslated sequence selected from the group consisting of proto-oncogene *c-myc*, cyclin D1, vascular endothelial growth factor, and ornithine carboxylase; whereby, in a metastatic tumor cell in which the presence of eukaryotic initiation factor eIF4E allows the translation of the toxin, the toxin is translated to kill the tumor cell; and whereby the majority of non-tumor cells in the

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mammal are not killed due to the low levels of eukaryotic initiation factor eIF4E typically present in non-tumor cells.

Claim 4. (withdrawn) A method as recited in Claim 1, wherein the encoded toxin is a conditional toxin.

Claim 5. (withdrawn) A method as recited in Claim 4, wherein the encoded conditional toxin is a herpes thymidine kinase; and wherein the method additionally comprises administering an effective amount of ganciclovir to the mammal; whereby, in a metastatic tumor cell in which the presence of eukaryotic initiation factor eIF4E allows the translation of herpes thymidine kinase, and in which ganciclovir is taken up by the cell, the translated herpes thymidine kinase in the cell phosphorylates the ganciclovir, allowing the phosphorylated ganciclovir to kill the tumor cell; and whereby the majority of non-tumor cells in the mammal are not killed due to the low levels of eukaryotic initiation factor eIF4E typically present in non-tumor cells.

Claim 6. (withdrawn) A method as recited in Claim 5, wherein the untranslated region comprises the 5' untranslated sequence of fibroblast growth factor-2.

Claim 7. (withdrawn) A method as recited in Claim 5, wherein the untranslated region comprises the 5' untranslated sequence selected from the group consisting of proto-oncogene *c-myc*, vascular endothelial growth factor, and ornithine decarboxylase.

Claim 8. (withdrawn) A method as recited in Claim 1, wherein the untranslated sequence comprises mRNA with a hairpin conformation having a stability of  $\Delta G \geq 50$  Kcal/Mol.

Claim 9. (withdrawn) A method as recited in Claim 1, wherein the metastatic tumor is associated with a mammalian cancer selected from the group consisting of bladder, breast, cervical, colon, prostate, and head and neck.

Claim 10. (currently amended) A DNA sequence comprising a promoter operatively linked to a transcription sequence; wherein the transcription sequence, when

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transcribed, produces a messenger RNA sequence that comprises a translatable sequence encoding a toxin, and an untranslated sequence; wherein the untranslated sequence inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E; wherein the untranslated sequence allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells; and wherein the untranslated sequence further comprises a hairpin secondary structure conformation having a stability  ~~$\Delta G \geq$  about 50 Kcal/Mol~~ measured as folded state free energy of  $\Delta G \leq$  about -50 Kcal/Mol.

- Claim 11. (Original) A DNA sequence as recited in Claim 10, wherein the untranslated sequence allows translation of the toxin sequence under conditions which exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E at least 2-fold greater relative to normal cells.
- Claim 12. (Previously presented) A DNA sequence as recited in Claim 10, wherein the untranslated sequence comprises the 5' untranslated sequence selected from the group consisting of fibroblast growth factor-2, cyclin D1, proto-oncogene *c-myc*, vascular endothelial growth factor, and ornithine decarboxylase.
- Claim 13. (Original) A DNA sequence as recited in Claim 10, wherein the encoded toxin is a conditional toxin.
- Claim 14. (Previously presented) A DNA sequence as recited in Claim 13, wherein the encoded conditional toxin is a herpes thymidine kinase.
- Claim 15. (Previously presented) A DNA sequence as recited in Claim 14, wherein the untranslated sequence comprises the 5' untranslated sequence of fibroblast growth factor-2.

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- Claim 16. (Previously presented) A DNA sequence as recited in Claim 14, wherein the untranslated sequence comprises the 5' untranslated sequence selected from the group consisting of proto-oncogene *c-myc*, vascular endothelial growth factor, and ornithine decarboxylase.
- Claim 17. (Cancelled).
- Claim 18. (Previously presented) A DNA sequence as recited in Claim 10, wherein the untranslated sequence comprises a G/C- rich 5'UTR sequence.
- Claim 19. (Previously presented) A DNA sequence as recited in Claim 18, wherein the untranslated sequence comprises mRNA with at least one substantially palindromic oligonucleotide sequence that is self-complimentary.
- Claim 20. (Previously presented) A DNA sequence as recited in Claim 10, wherein the conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells are those that exist in metastatic tumor cells.
- Claim 21. (Currently amended) A messenger RNA sequence that comprises a translatable sequence encoding a toxin, and an untranslated sequence; wherein the untranslated sequence comprises an mRNA sequence with a secondary structure conformation having a stability  ~~$\Delta G \geq \text{about } 50 \text{ Kcal/Mol}$~~  measured as folded state free energy of  $\Delta G \leq \text{about } -50 \text{ Kcal/Mol}$  and wherein the untranslated sequence inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and wherein the untranslated sequence allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells.
- Claim 22. (Previously presented) A vector comprising the DNA sequence of claim 10.

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Claim 23. (Previously presented) The vector of claim 22, wherein the vector is a viral vector.

Claim 24. (Previously presented) The vector of claim 22, wherein the vector is a non-viral vector.

Claim 25. (Previously presented) The vector of claim 23, wherein the vector is a BK vector.

Claim 26. (Previously presented) A pharmaceutical composition comprising a therapeutically effective amount of the vector of claim 22 and a carrier.

Claim 27. (Previously presented) The pharmaceutical composition of claim 26 wherein the carrier is a liposomal complex.